PB80-213861

Lindane
Position Document 1

(U.S.) Environmental Protection Agency
Arlington, VA

17 Jan 77

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EPA/SPRD - 80/43

Lindane Working Group
U.S. Environmental Protection Agency

17 JAN 1977

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50272-101

REPORT DOCUMENTATION PAGE	1. REPORT NO. EPA/SPRD-80/43	2.	3. Recipient's Accession No. PB 80 213861
4. Title and Subtitle Lindane: POSITION DOCUMENT 1			5. Report Date 1/17/77 6.
7. Author(s)			8. Performing Organization Rept. No.
9. Performing Organization Name and Address Special Pesticide REview Division ENvironmental Protection Agency Crystal Mall 2 Arlington, VA			10. Project/Task/Work Unit No. 11. Contract(C) or Grant(G) No. (C) (G)
12. Sponsoring Organization Name and Address Environmental Protection Agency 401 M St. S.W. Washington, D.C. 20460			13. Type of Report & Period Covered 14.

15. Supplementary Notes

16. Abstract (Limit: 200 words)

Preliminary Risk Assessment: Examination of possible unreasonable risks associated with uses of pesticide and a gathering of all available information to determine whether or not this or any other risk does exist. Initiates literature search and evaluates risk data. Limited information on exposure to forecast extent of risk.

17. Document Analysis a. Descriptors

0504,0606,0703

b. Identifiers/Open-Ended Terms

c. COSATI Field/Group

18. Availability Statement: Release Unlimited	19. Security Class (This Report) Unclassified	21. No. of Pages
	20. Security Class (This Page) Unclassified	22. Price

(See ANSI-Z39.18) See Instructions on Reverse

OPTIONAL FORM 272 (4-77)
(Formerly NTIS-35)
Department of Commerce

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LINDANE: POSITION DOCUMENT 1

SUMMARY

Technical lindane is at least 99% gamma-BHC, the remainder being other BHC isomers. The insecticidal properties of benzene hexachloride (BHC) were discovered and developed for commercial use in pest control in 1942. When it was found that virtually all the insecticidal activity of BHC resided in the gamma isomer, major development of the latter as the insecticide called lindane was rapid. Lindane has had major use in insect control in domestic and commercial settings, in numerous agriculture and silvaculture applications, and as dips, sprays, and dusts for livestock and pets. There are currently 557 federal registrations for pesticide products containing lindane and 87 formerly state-registered products containing lindane for which federal registration has been requested.

In 1969, the Department of Health, Education, and Welfare (HEW) recommended in the Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health (Mrak Report), that the usage of lindane, along with that of other named persistent pesticides, be restricted to specific essential uses which create no hazard to human health or to the quality of the environment and which are unanimously approved by the Secretaries of the Departments of Health, Education, and Welfare; Agriculture; and Interior (1). It was noted that these pesticides cause or can cause contamination of the environment and damage to various species within it.

Monitoring data show that lindane occurred in 0.77, 1.56, and 0.56% of samples collected during the years 1970, 1973 and 1974, respectively. The geometric mean level of lindane in the adipose tissue of the general population for the years 1970 to 1974 was less than 0.1 ppm on a lipid basis.

Residues between 0.3 and 16.2 ng/m^3 were found in ambient air samplies in 5 U.S. cities in 1976. Lindane residues have been found in rainwater and drinking water. Residues detected in the HEW-USDA Market Basket Survey of foodstuffs have been well under the average daily intake level deemed acceptable by the Food and Agricultural Organization of the World Health Organization.

The possibility exists that isomerization of lindane, gamma-BHC, to other isomers takes place under certain conditions.

Lindane accumulates in tissues, although not to the same extent as many other chlorinated hydrocarbon insecticides. Upon cessation of feeding much of the lindane appears to be eliminated from the bodies of laboratory rodents in the form of substances of relatively low toxicity.

Administrative actions resulting in cancellation have been taken against the registration of lindane products for certain uses including "continuous" vaporizers, use on certain agricultural crops and dairy cattle, and in dairy barns and milk rooms. The use of "one-shot" lindane vaporizers is still registered.

Adequate scientific evidence exists to initiate the rebuttable presumption against the registration of all pesticide products containing lindane on the basis of oncogenicity, chronic reproductive and fetotoxic effects, and acute effects on aquatic organisms.

A number of human pesticide accidents involving lindane have been reported. Hemotoxic effects in humans and possible reproductive effects in nontarget avian species have been noted and are described in this position document. These effects have not been used to initiate the rebuttable presumption, but additional data will be solicited in the Rebuttable Presumption Against Registration Federal Register Notice. (See Sections III. B., C., and D.)

Registrants of lindane products will be directed to certify to the Agency their determination as to whether the formulations registered for use meet or exceed the acute dermal and inhalation criteria of 162.11(a)(3)(i)(A).

I. BACKGROUND

A. Environmental Chemistry

(1) General

Lindane is the gamma isomer of the insecticidal chemical benezene hexachloride, BHC. Technical lindane must contain at least 99% gamma-BHC, the remainder being other BHC isomers. End-use insecticide products contain varying percentages of active ingredient.

Benzene hexachloride (BHC) is the common name used to designate the mixed isomers of 1,2,3,4,5,6-hexachlorocyclohexane, although 1,2,3,4,5,6-hexachlorocyclohexane is the proper term for these isomeric compounds. BHC (technical grade) is a mixture of the eight possible isomers which constitute the different spatial orientations of the six chlorine atoms on the chair form of the cyclohexane ring.

Its composition approximates 65% alpha, 11% beta, 13-14% gamma, 8-9% delta, and 3-5% other isomers. Technical BHC is commonly prepared by photochlorination of benzene. Production of the gamma isomer for lindane is achieved by selective extraction (2).

(2) Residues

The presence of lindane in sites far removed from any application suggests that this chemical has world-wide distribution.

Lindane residues have been found, for example, in rainwater samples from several countries (see Section I.A.(2)(b)), in birds, penguins, skuas, and cormorants; fish, Nototheria sp.; and planktonic krill in Antarctica (3); and in seals and an arctic fox in Greenland (4).

(a) Water

Lindane, which is soluble in water at 10 ppm, is one of the most soluble of the chlorinated hydrocarbon insecticides. From February 1975 through June 1976, the National Water Monitoring Program's survey of unfiltered water samples detected lindane in only a single sample from Hawaii at a level of 0.01 ug/liter. About 850 water and 425 bottom sediment samples collected from sites throughout the nation have been analyzed for lindane since the start of this survey (5).

Laboratory examination of drinking water from various sources across the United States by EPA's Water Supply Program revealed that, of 684 samples tested for pesticide residues, lindane levels of <0.001 ug/liter were found at 37 sites, <0.100 ug/liter at 16 sites, 0.160 ug/liter at 1 site, 0.200 ug/liter at 1 site, and 0.900 ug/liter at 1 site (6).

(b) Air

Lindane has a vapor pressure of 9.4×10^{-6} mm Hg at 20° C and is more volatile than most of the commonly occurring organochlorine pesticides. During the years 1970 to 1972 lindane residues were found in 68% of 2,479 ambient air samples from 14 to 16 selected states. The arithmetic mean for all samples was 0.6 ng/m^3, and the mean for positive samples was 0.9 ng/m^3. In 1976, however, lindane was present at higher levels in ambient air samples in some regions of the country. Relatively high residue levels of alpha-BHC were also found. Alpha isomer residues are relevant to our concern about lindane-use if isomerization of lindane is taking place in nature

(see Section I.A.(2) and I.C.). The levels detected for alpha-BHC and for lindane (gamma-BHC) were, respectively, 2.6 and 2.2 ng/m^3 in Miami, Florida; 18.9 and 0.3 ng/m^3 in Fort Collins, Colorado; 2.9 and 0.5 ng/m^3 in Lafayette, Indiana; 3.5 and 16.2 ng/m^3 in Jackson, Mississippi; and 4.3 and 0.4 ng/m^3 in Harrisburg, Pennsylvania (7).

Lindane has also been detected in rainwater in several countries. Lindane residues were found in rainwater in the British Isles over a 12-month period with a mean of 44 parts per 10^{12} water (8). Lindane at levels of 46 to 404 nanograms per liter of rainwater was present in all of 12 samples of rainwater taken over the city of Berlin Dahlem, West Germany during a 1-year period, June 1970 to May 1971 (9).

Traces of BHC were found in 34 of 90 rainwater samples from 3 Ohio sites (10). This study noted that recent evidence had shown that reported pesticide concentrations in rainwater were low, perhaps by a factor of 2, because the method used to collect samples resulted in incomplete recovery.

(c) Soil

Lindane is eliminated from soil at faster rates than most other chlorinated hydrocarbon insecticides but is persistent when compared with other classes of pesticides. Soil treated with lindane and analyzed over a 15-year period showed 0.2% of the lindane remaining at the end of that time (11). A similar test in the Netherlands showed 3 to 8% of the lindane remained in soil test areas after 15 years (12). Available data indicate, however, that lindane residues in soil are low. EPA's National Soils Monitoring Program has reported that lindane has seldom been detected in soils sampled. In 1969, 0.9% of the 1,729 cropland sites sampled had detectable lindane residues. Levels found were between 0.1 and 0.035 ppm. In 1970, the percentage of cropland sites with detectable lindane residues fell to 0.4% of 1,506 cropland sites sampled, and lindane residues varied between 0.01 and 0.15 ppm. The program was not operated in 1971. In 1972 and 1973 no residues were detected (13).

(d) Plants & Animals

Results from lindane residue surveys indicate that low levels of lindane are present in some plant and animal populations. The amount found in plants depends upon many factors including the crop and the soil type.

Lindane residues have been found in natural bird populations. Watson and Morgan (14) reported the following lindane residues in the carcass of a golden eagle found in Scotland in 1963: 0.05 ppm in brain, 0.14 ppm in fat, 0.66 ppm in muscle, and 0.02 ppm in liver. Birds of prey and owls found dead or dying in the Netherlands during 1964 had considerably higher lindane residues than usually reported in these birds (22). Levels found were: liver, 0.5 to 28.6 ppm; brain, 3.2 to 17.7 ppm; breast muscle, 1.6 to 18.4 ppm; and mesenterial fat, 11.0 to 89.3 ppm. Linder and Dahlgren (15) analyzed lindane levels in the eggs and adult tissues of wild pheasants collected in eastern South Dakota between 1964 and 1969. In this study it was found that eggs taken from three different areas at two different periods (early May and late June)had levels of lindane ranging from 0.01 to 0.04 ppm but lindane residues were detected in trace amounts (<0.05) in the tissue of only 2 of 100 birds examined. Over seventy-five percent of the grouse and pheasants analyzed in the central portion of South Dakota between 1965 and 1967 had 0.01 ppm lindane residues or less, and the remainder had less than 0.20 ppm (21). Greichus et al. (16) found lindane residues of 0.07 ppm in muscle and 2.8 ppm in fat of pelicans and cormorants which were part of the food chain of a freshwater lake.

Starlings collected from 128 sites throughout the U.S. during 1967 and 1968 had lindane residues between zero and 1.25 ppm. Most residues were below 0.02 ppm, and only two were over 1 ppm (20).

Analyses of wings of black ducks and mallards taken along all major U.S. flyways have shown an increase in lindane residues in recent years. During the 1965-1966 hunting season, trace amounts of lindane were found only in some of the birds killed in Washington and Michigan (17). During the 1969-1970 season, no lindane residues were detected (18). In the 1972-1973 hunting season, however, 75% of all black ducks and mallards taken had lindane present in trace amounts in their wings (19).

Lindane residues have also been found in birds and their eggs following laboratory feeding. Liska et al. (23) sprayed a grass-covered range with 0.1% lindane emulsion at a rate of 0.5 lb/acre and assayed lindane residues in groups of turkeys placed on the range at different intervals after the pesticide was applied. Lindane was found at 2.1 ppm in the fat of turkeys placed on the range immediately after spraying, at 1.0 ppm in turkeys placed on the range one week after spraying, and at 0.7 ppm in turkeys placed on the range two weeks after spraying. Similarly, Stadelman et al. (24) reported that feeding turkey hens 0.1 to 0.15 ppm lindane-treated seed for 14 days resulted in only transient traces of lindane in tissues, but that when 10 to 15 ppm lindane was supplied in the feed for 5 days, lindane residues were found in body fat and eggs for 10

weeks. Stadelman (25) reviewed studies published between 1961 and 1972 which reported the occurrence of lindane residues in avian tissues and eggs.

In another experimental study, Ash and Taylor (26) assayed lindane residues in pheasant eggs and adult tissues. Twenty-four birds were fed lindane-dressed seed for 82 days. Lindane levels on the seed ranged from 52 to 117 ppm. The authors estimated that each bird consumed approximately 0.5 mg lindane per day and that the 430 eggs laid during the experimental period contained an average of 10.7 ppm lindane indicating that some of the dietary pesticide was excreted via the egg. Within 9 days, 2/3 of the initial lindane residues had been excreted.

A test (27) in which pheasants were fed as much ^{14}C-lindane treated seed as they would eat in one day (an estimated 9.00 to 14.75 mg of lindane per bird) resulted in lindane residue levels of 1.12 and 2.48 ppm in muscle and liver, respectively, one day later. These levels, however, decreased very rapidly, and no residue could be detected after 14 days. The ingestion of less lindane- (525 to 860 seeds) than heptachlor-treated seed (590 to 1240 seeds) was believed due to less palatability of the lindane-treated seed.

This result was also noted in the Ash and Taylor study (26) which demonstrated that pheasants are very reluctant to eat lindane-treated grain. In this laboratory test, pheasants would ingest lindane-treated seed only after they were gradually conditioned to eat larger amounts of pesticide in their diet, and then only when the application rate was reduced to 1/3 the normal dose. These pheasants still consumed 14% less seed than the controls.

Some research suggests that birds may be killed by lindane but that detected residue levels may not reflect the cause. French and Jefferies (28), for example, demonstrated that during the first 24 hours after death degradation of lindane occurs rapidly in the liver of laboratory pigeons force-fed gelatin capsules containing lindane. Residues were found in the livers of 3 pigeons killed after being fed 60 mg/kg lindane for 72 hours and 2 pigeons which died after being fed 225 mg/kg lindane for 144 hours. Initial liver residues after death in one of the high dosage birds was 153 ppm. By the end of 430 hours, the residue level fell to 2 ppm. Lindane residues in the liver of the second high dosage bird, which were not measured at death, were 4 ppm at 430 hours. Rapid degradation of lindane residues also took place in the livers of the low dosage pigeons. Residues measured one day after death had fallen to almost half of the initial level measured immediately after death and continued to decline thereafter (28).

The 1972-1973 results of the fish monitoring program conducted by the Fish and Wildlife Service, USDI, indicated that BHC, including lindane, was in the group of pesticides which were found in 3% or less of the samples taken during those two years (29). A study by Gakstatter and Weiss (30) reported that within 2 days after being placed in clear water the initial lindane residues had been eliminated by 2 species of fish, bluegills and goldfish, exposed to water containing 0.03 ppm lindane for 32 days.

From October 1968 to July 1970, shellfish from 10 estuaries in Long Island, N.Y., were collected monthly and examined for chlorinated hydrocarbons as part of a continuing nationwide survey conducted by the National Marine Fisheries Service of the U.S. Department of Commerce. No lindane residues were found (31).

There are few lindane residue studies in mammals in nature. Lindane residues between 0.1 and 0.08 ppm were found in 17 of 47 large game animals taken in South Dakota (32). It was noted that there was only limited use of lindane in South Dakota.

Lindane residues have also been found in the adipose tissue of arctic animals killed in 1972 on the west coast of Greenland (4). Lindane was detected in 5 bearded seals, 0.007 to 0.64 ppm, 2 ringed seals, 0.002 and 0.025 ppm, 1 hooded seal, 0.017 ppm, and an arctic fox, 0.010 ppm.

In general, lindane storage in the fat, milk, and eggs of animals is less than that of other chlorinated hydrocarbon insecticides.

(e) Food

The World Health Organization (WHO) and the Food and Agricultural Organization (FAO) of the United Nations have set an acceptable daily intake (ADI) for lindane of 1.25×10^{-2} mg per kg body weight. The ADI is a dosage (as determined by WHO/FAO) which, if ingested daily for the lifetime of an individual, is assumed to be without appreciable risk. HEW's "Market Basket Survey," conducted by the Food and Drug Administration in cooperation with the Department of Agriculture, monitors cetain pesticide residues in the sample daily diet of an average 16-to-19-year-old American male in various regions of the country. Lindane residues in the diet as measured under these Market Basket Surveys have been considerably lower than the WHO/FAO acceptable levels. For the five-year period from 1964 to 1969, the average daily dietary intake of lindane was 5.0×10^{-5} mg/kg according to the FDA Market Basket Survey. In general, the highest residues in food intended for human consumption appeared, in descending order, in meat, grain and cereals, dairy products, eggs, and poultry.

The incidence and the amount of lindane residues in foodstuffs varied. Only trace amounts, <0.005 ppm, were found as an average in raw products of most food groups during the 5-year period. Levels above trace amounts in these raw products were found in the fat of imported dairy products, 0.02 ppm; in domestic tree nuts, 0.01 ppm; and in domestic and imported meat in 1968-1969 only, 0.01 ppm (114).

The average of most lindane residues found in samples of ready-to-eat foods from the major food groups were below 0.001 ppm, but the average for vine and ear crops was 0.002 ppm; for the grains and cereals group, 0.006 ppm; and for meat fat for 1968-1969, 0.1 ppm (114).

It must be remembered that these figures represent an average which individual samples exceeded and that risk of ingesting lindane may be different for certain segments of the population because of such factors as diet and susceptibility. In 1968, for example, lindane was present in poultry meat at levels of 0.01 to 3.0 ppm in 10.6% of 2,679 samples; in 1971, lindane levels of 0.01 to 0.5 ppm were reported in 5% of 1, 904 samples. This represented a reduction in the lindane level and in the proportion of samples with residues during this 3-year period (109).

More recently, lindane residue levels in food have dropped (33). In 1973, although detectable amounts were found in 10.8% of all samples, only 2.22×10^{-4} mg/day was present in the diet of an average 16-to-19-year-old male. This is equivalent to 0.32×10^{-5} mg/kg body weight per day, which is less than the 5.0×10^{-5} mg/kg/day found during 1964 to 1969. In 1974, lindane residues were found in 14.4% of all FDA Market Basket samples. These food residues resulted in a human consumption rate of 0.84×10^{-5} mg/kg/day.

(e) Humans

In addition to food sources, the total human body burden may be increased by residues in household dust, in fish and other seafood caught by the consumer, in game animals, in drinking water, in vegetables from the home garden, and from inhalation.

Monitoring data, collected by EPA's National Human Monitoring Program, show that lindane in human adipose tissues occurred in 0.77, 1.56, and 0.56% of samples collected during the years 1970, 1973, and 1974, respectively. The

geometric mean level of lindane detected in adipose tissue from the general population for the years 1970 to 1974 was less than 0.1 ppm on a lipid basis (34).

B. Metabolism

Lindane can be found in the body organs and tissues of mammalian, avian, and aquatic species with the greatest storage in body fat. It has been established that lindane is deposited in body lipids at the same concentration as that found in the diet (35).

Lindane is, however, eventually metabolized in various organisms to much less toxic water soluble products which are then excreted in the urine. (The available data were summarized by Menzie (36), (37)).

Mammalian biotransformation of BHC isomers involves the formation of chlorophenols (trichloro-, tetrachloro-, and pentachloro-) which are excreted free and as conjugates of sulfuric and glucuronic acids (38), (39). The eliminated products, the free and conjugated chlorophenols, are of much lower toxicity than the parent isomers, and some are being considered separately as contaminants in water.

Many metabolites of lindane have been reported in the literature reviewed by the Working Group. Some of the metabolites were chlorophenol and chlorobenzene compounds which appeared in the 1974 edition of HEW's Toxic Substances List (110).

In December 1975, EPA's Office of Toxic Substances submitted to Congress a preliminary assessment of suspected carcinogens in drinking water. There were 253 organic chemicals, most not implicated as carcinogens in that publication, which have been found in drinking water samples in this country (110).

Several chlorophenols and o-Dichlorobenzene were the only lindane metabolites of those identified in the literature reviewed by the Working Group which appeared in the above list of substances found in drinking water. It was observed, however, that because of limited sampling and the restrictive nature of analytical systems, the drinking water list was not definitive nor indicative of continuous occurrence. The highest reported level for these metabolites was for 2,4-Dichlorophenol at a concentration of 36 ug per liter of water (110). This high level at one site is not surprising as chlorophenols are readily produced by the addition of chlorine to water containing phenol (111).

The possibility of the occurrence of lindane metabolites as the result of other natural and human-influenced chemical processes in water and other media complicates an assessment of the role of lindane in any hazard from these substances. An approved health limit for lindane of 0.004 mg/liter of drinking water has been set by EPA's Water Supply Division (111).

The Lindane Working Group has not as yet thoroughly investigated the environmental and human health hazards from lindane metabolites. Data will be reviewed by the Working Group during the Rebuttable Presumption Process to determine if any of the known lindane metabolites can be shown to add substantially to the hazards associated with the use of products containing lindane. Among the data to be reviewed, if available, will be a study by the National Academy of Sciences which is being conducted to provide health data for setting maximum contaminant levels for drinking water. This study was arranged by EPA's Office of Toxic Substances (111), and is now scheduled for completion in March 1977.

C. Studies on the Isomerization of Gamma-BHC to the Alpha and Beta Isomers

Separate scientific studies indicate that the alpha and beta isomers of BHC are oncogenic in rodents and that the gamma isomer may isomerize to the alpha and beta forms. This suggests that in addition to the adverse properties inherent in the gamma isomer, lindane may also have additional adverse effects based on the alpha and beta isomers, which may be formed as isomerization products of the parent gamma isomer.

The relative thermodynamic stabilities of the four major BHC isomers in order of increasing thermodynamic stability are as follows: gamma<alpha<delta<beta. Moreover, stability to ultraviolet radiation is in the order delta< gamma<alpha<beta. Accordingly, in theory if there were a reaction uniformly capable of converting BHC isomers, the alpha and beta isomers would eventually predominate in systems originally containing only gamma. In other words, there are thermodynamic and photochemical driving forces in favor of the alpha and beta isomers as against the gamma form. Empirical support for isomerization has been developed in several laboratory studies which indicate that under defined environmental conditions gamma-BHC isomerizes to the more stable isomers. Newland et al. (40) reported that in the anaerobic environment of a simulated lake impoundment an estimated 3.3% of the gamma isomer is tranformed to alpha-BHC and, to a lesser extent, delta-BHC before metabolic degradation occurs. The corresponding figures for conversion from gamma- to alpha-BHC under aerobic conditions are 0.2 to

1.0%. Because aeration influenced the reaction rates, the investigators assumed that isomerization proceeded through a biological mechanism; the responsible organisms were not isolated or identified.

Studies by Benezet and Matsumura (41) on the fate of the gamma isomer in aquatic sediments indicate that the alpha isomer is present in excess of the levels which would be expected if gamma-BHC were not converted to the alpha form by isomerization. In a subsequent study Matsumura et al. (42) isolated a soil organism, Pseudomonas putida, which isomerizes the gamma isomer and is ubiquitous in lakes, soil, and sediments. Kamada (43) seperately administered the alpha, gamma, and delta isomers of BHC to rats by intubation. Subsequent analysis of the rat tissues revealed accumulation of alpha-BHC and beta-BHC, indicating that isomers tend to convert to alpha and beta[1/]

Studies indicating that gamma-BHC may isomerize to the alpha and beta isomers make the data which establish that the alpha and beta isomers are oncogenic and fetotoxic to rodents relevant to assessment of lindane's toxic properties. These studies report that the alpha and beta isomers of BHC induce statistically significant oncogenic changes in 7 different rat and mouse strains. IARC has evaluated these studies and concluded that "(t)echnical BHC, its pure alpha, beta and gamma isomers and the mixture of delta plus epsilon isomers are carcinogenic in mice, producing liver-cell tumors following oral administration" (45). These studies formed the basis for the issuance of a rebuttable presumption against reregistration of BHC in part on grounds of the oncogenicity of BHC and its alpha and beta isomers. They are summarized in that notice and the accompanying position document.

Although the Working Group is aware that there are degradation and metabolism studies which have neither detected isomerization of gamma-BHC nor found unidentified products, we believe that the positive studies nevertheless provide a basis for concern that lindane may possess some of the toxic properties of the alpha and beta isomers. The Agency is presently examining monitoring data which show unexplained and unanticipated high levels of alpha-BHC in ambient air (See Section I(A)(2)b) and beta-BHC in adipose tissue; these data may be supportive of studies indicating isomerization. Further studies on the extent of *in vivo* and environmental isomerization as well as additional confirmatory analytical tests may be necessary.

1/ Dr. Chadwick, an EPA scientist who has done research on *in vivo* metabolism of lindane, questioned the techniques and conclusions arrived at in Kamada's *in vivo* isomerization study (44), (43).

D. Regulatory History

In 1969, HEW recommended in the Mrak Report (1) that the usage of lindane, along with that of other named persistent pesticides, be restricted to specific essential uses which create no hazard to human health or to the quality of the environment and which are unanimously approved by the Secretaries of the Departments of Health, Education, and Welfare; Agriculture; and Interior. It was noted that these pesticides cause or can cause contamination of the environment and damage to various species within it.

In April 1969, pursuant to a General Accounting Office (GAO) report to Congress, the Department of Agriculture, USDA, cancelled the registration of lindane insecticide products intended for vaporization. Questions regarding the safety of these products had been raised repeatedly since the first registrations were made in the early 1950s, but prior to the cancellation decision USDA had concluded that there was little evidence either to support definitive proof of safety or to demonstrate a genuine hazard from the products when used as directed.

Under recommendations of the General Accounting Office, the Secretary of Agriculture appointed a Medical Advisory Panel to review USDA's previous cancellation decision. The panel carefully considered the association of blood dyscrasias with lindane vaporizers, the ability of lindane vapor to penetrate and persist in foods (unless they were sealed in metal or glass), and the availability of less persistent but equally effective insecticides. The Medical Advisory Panel confirmed the original decision, concluding that the use of lindane by automatic vaporization techniques should be discontinued because it creates a potential hazard to human health. USDA thereupon reaffirmed its original cancellation decision. Some registrants then requested that an independent advisory committee consider the relative hazard of these products. This advisory committee was convened and recommended on July 2, 1970, that the cancellation be maintained.

At the request of some registrants, public hearings were held June 23 through 29, 1971. Separate hearings were held to consider the cancellation of "continuous" vaporizers and of "one-shot" vaporizers. In both cases the Hearing Examiner recommended that the cancellations be withdrawn, but the EPA Judicial Officer issued an order which disagreed with those recommendations. One continuous vaporizer product was immediately cancelled. Others were restricted to commercial use with labels modified accordingly. One-shot vaporizer labels were amended to prohibit use in areas where food is prepared, stored, sold, processed, or otherwise handled.

Appeals by the registrants resulted in stays of each order by U.S. Courts of Appeal pending further direction from the courts. On May 11, 1972, the U.S. Court of Appeals for the 7th Circuit ruled in favor of Continental Chemiste Company, the sole registrant for one-shot vaporizers, and sales of three of this company's lindane products were allowed to continue without label restrictions. (461 F. 2d 331 (7th Cir., 1972.)) These products are still being produced and sold. On December 6, 1972, the U.S. Court of Appeals for the 8th Circuit upheld the Judicial Officer's order with regard to the two "continuous" lindane vaporizer products.

Another lindane household product, treated shelf paper, was first cancelled after USDA Agricultural Research Service tests indicated that continuous use of lindane or chlordane treated shelf paper may produce residues in home-stored food, and the Food and Drug Administration recommended against further use of these products. USDA then cancelled the registrations of all lindane and chlordane impregnated shelf paper on November 18, 1969. At that time, USDA believed that label restrictions were inadequate to prevent use in food storage areas. However, upon recommendation of an internal Hazardous Materials Advisory Committee, EPA, which had assumed the pesticide regulatory function from USDA, later withdrew the original order and permitted use with certain labeling requirements.

Tolerances of 0.01 to 7 ppm for lindane have been set on a variety of forage crops, dairy products, poultry, and raw meat from domestic animals including cattle, sheep, hogs, and chickens. Some of the original tolerances were reduced, primarily so they would comply with the policy that residues should be no higher than the amount reasonably expected to result when directions for use are followed (46).

The Food and Drug Administration enforces "action levels" for pesticide residues on raw agricultural commodities and processed foods for which formal tolerances have not been granted. These action levels represent residue levels at which legal action can be taken to prohibit sale or use of the commodity; the FDA may take action at lower residue levels if there is evidence of pesticide misuse or if some other factor appears to warrant such action. The following action levels have been established for lindane: 4.0 ppm for poultry fat, 0.5 ppm for eggs and some fruits and vegetables, 0.3 ppm (on a fat basis) for butter, raw unpasteurized milk, and all manufactured dairy products including pasteurized or otherwise processed milk, and 0.1 ppm for grains (47).

On February 1, 1968, all registered uses of lindane on the following crops, which had been assigned a zero lindane residue tolerance as a safe level, were cancelled by USDA: blueberries, birdsfoot trefoil, buckwheat, currants, endive, gooseberries, pasture and range grass, lespedeza, pecans, sweet potatoes, pimentoes, and walnuts. In addition, all registered lindane uses, except seed treatment, were cancelled on the following products: alfalfa, clover, cotton, flax, oats, rye, sorghum, soybeans, sugar beets, and wheat. In the event that any crops had been left out of this category, the notice also specified that all lindane uses except seed treatment on all field, forage, fiber, and grain crops were cancelled (48). The registered uses on dairy cattle, dairy barns, and milk rooms which were cancelled by this notice were extended on January 19, 1970, by a temporary exemption from cancellation. On March 12, 1971, these uses were cancelled (49). Following FDA cancellation of tolerances for lindane and BHC on beans, citrus, corn, and peas, USDA cancelled the registration of these insecticides on February 26, 1970, for those uses and for the post-harvest application of lindane vapor to lemons in storage (50).

On March 18, 1971, the Administrator announced that EPA had begun an extensive internal review of three persistent pesticides (BHC, lindane, and endrin) to determine if any uses of these compounds presented a substantial question of safety. Accordingly, an EPA Special Pesticide Review Group conducted a review of the hazards associated with the use of lindane, completing a report in August 1973. This report was primarily a literature review and compilation of current research; no recommendations were made at that time regarding continued registration. There was, however, a brief discussion of relative risks and benefits resulting from broad usage patterns. No regulatory action resulted.

On November 27, 1974, the Criteria and Evaluation Division (CED), using information derived in the 1973 review, recommended that the use of lindane in feed bins be cancelled because of the potential for producing residues in milk. No other lindane uses were recommended for cancellation. However, gradual phaseout was recommended for all uses of BHC.

This recommendation observed that, in general, studies reviewed indicated that "high levels of lindane may not be expected to present a carcinogenic hazard to man when used as a pesticide on food crops." It was further observed that "lindane is not occurring as residues in man, his food or his environment in amounts sufficient to warrant concern." The use of shelf paper in accordance with EPA recommended label changes was believed not likely to result in excessive residues.

A notice of intent to cancel all BHC uses and the use of lindane in cattle food bins was drafted but not sent to the Administrator (51).

On December 1, 1975, the Health Research Group (HRG) petitioned the Administrator to take immediate action against all lindane aerosol products by issuing a notice of suspension and cancellation and by requiring a recall and seizure of existing stocks (52). Consumer confusion and potential hazard due to the labeling of one registrant's lindane products were primarily at fault. The virtually identical labeling of low percentage lindane aerosol cream, lotion, and shampoo for control of lice on humans and of the same manufacturer's higher percentage lindane aerosol product for use on inanimate objects presented the possibility of accidents. In response to the HRG petition, the Registration Division, OPP, directed the registrant to change its product label which would, in effect, reduce accidental exposure to humans. The Health Research Group subsequently withdrew its petition.

E. Registered Uses and Production

Pesticides containing lindane have been federally registered since the early 1950s although the insecticidal properties of lindane were known before that time. Current registrations include uses for home and garden; seed treatment; foliar and soil applications to fruit and vegetable crops, ornamentals, lawn and turf; borer control in fruit and ornamental trees; control of pests on livestock and pets; and control of human parasites. The records in the Registration Division, OPP, show registrations for 557 lindane products distributed among 267 federal registrants. There were 87 applications for federal registration of formerly intrastate registrations by 48 companies.

Lindane products are formulated as wettable powders, emulsifiable concentrates, dry powders, liquids, and pressurized products, including "one shot" vaporizers and aerosols. Hooker Chemicals and Plastics Corporation of Niagara Falls, New York, was the sole domestic manufacturer of lindane. In May 1976, however, Hooker temporarily halted production of lindane, and all manufacturing-use lindane has been imported since that time.

Section 7(c) of FIFRA requires manufacturers and formulators to submit to EPA information on production, sales, and distribution. Under FIFRA sections 7(c) and 10 this information may not be made available to the public. A confidential memorandum containing this information has been sent to the Deputy Assistant Administrator for Pesticides (53).

Current EPA records indicate that 242 registrants of lindane products reported production and distribution data to this Agency. Within this group less than 25 lb of actual lindane was formulated for each of 39 end-use products, and 40 products were not produced at all. Of the 555 registered products containing lindane, the formulators for 313 products did not report production and distribution data. Most products in this group are no longer being produced.

Agricultural end-use data was obtained from the National Study of Agricultural, Governmental, and Industrial Uses of Pesticides conducted by this Agency (54). These data indicated the following uses of lindane in the United States in 1974:

Crop	lb active lindane applied	% total agriculture
cucumbers	68,250	18.26
cattle	61,275	16.39
squash	53,025	14.19
swine	11,660	3.12
pineapples	7,274	1.95
ornamentals	6,244	1.67
nursery	2,510	0.67
corn	2,241	0.60
sheep	1,632	0.44
vegetables (misc. principally cucumbers)	1,000	0.27
seed treatment (peas, alfalfa, watermelon, wheat, barley, oats, sorghum, corn)	158,638	42.44
mushrooms	50	—
turf	8	—
safflower	2	—
estimated total use in agriculture for 1974	373,809	100

In addition, this survey reported that 5,127 lb of active lindane were used by federal and state agencies and 11,098 lb by industry.

It should be noted that these totals represent the minimum amount of lindane used on the listed sites. The protocol for implementing this study required that the pesticide uses on the seven leading crops in each state be identified, and the estimates were developed from this point. Therefore, pesticides applied to minor crops in each state were not identified, nor were the amounts used included in these estimates. Home and garden use of lindane was not reported.

The International Trade Commission reported that 65,805 lb of lindane was imported into the U.S. in 1966. There was no reported U.S. importation of lindane between 1967 and 1971. In 1972, however, importation totaled 132,939 lb but dropped to 5,757 lb in 1973 and 3,525 lb in 1974 (55), (56).

II. SUMMARY OF SCIENTIFIC EVIDENCE TO SUPPORT REBUTTABLE PRESUMPTION

The following adverse effects of lindane have been found to exceed the criteria for issuance of a Rebuttable Presumption.

A. Chronic Toxicity

(1) Oncogenic Effects in Test Animals

40 CFR Section 162.11(a)(3)(ii)(A) provides that "a rebuttable presumption shall arise if a pesticide's ingredient(s) . . . (i)nduces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation, or dermal exposure. . . ." Section 162.3(bb) defines the term oncogenic as "the property of a substance or a mixture of substances to produce or induce benign or malignant tumor formation in living animals."

Although the 1969 HEW Mrak Report (1) recommended severe restriction of lindane usage, lindane was not among the possible oncogenic agents cited in that report. Nor was lindane among the 120 compounds tested earlier in 1969 for tumorogenicity by the National Cancer Institute. Lindane was, however, listed as a suspected carcinogen in the more recent Suspected Carcinogens: A Subfile of the NIOSH Toxic Substances List (57).

The recent scientific literature includes six subacute studies (duration of exposure to a pesticide less than one-half the normal lifespan of the organism) and four long-term studies assessing the oncogenic effects of gamma-BHC in mice and rats. Three studies reported that lindane-feeding induced benign tumors, and one of these studies also described metastatic invasion of the lungs from tumors. Seven studies reported that lindane feeding did not induce oncogenic changes. In a 1973 report, the International Agency for Research on Cancer (IARC) Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Man reviewed these studies and concluded that gamma-BHC was carcinogenic in mice because it produced liver cell tumors following oral administration. This group also concluded that the available feeding studies in rats were inconclusive either because dosages or survival rates were low or because the published reports did not include sufficient information (45).

The Criteria and Evaluation Division (CED) of the EPA's Office of Pesticide Programs reviewed several of these studies (58), (59), (60) (61), and concluded that none of the presented data was adequate to initiate an RPAR. This conclusion was based on the reasoning that the studies were limited to mice, that the only tumor type to increase was hepatoma, and that the toxic effects evidenced by the high early mortality rate suggested that the hepatomas resulted from non-specific toxic effects due to high workload on the liver (62).

There was, however, misunderstanding at this time as to CED's role. The proper function of CED in the Rebuttable Presumption procedures now established is to determine whether the research conducted is scientifically valid, not whether submitted tests constitute adequate evidence to initiate an RPAR. The latter function is the role of the Working Group for a particular pesticide.

The EPA's Carcinogen Assessment Group (CAG) reviewed this same research and concluded that the procedures followed were scientifically valid and that the results obtained supported the research papers' conclusions that lindane induces oncogenic changes in mice as a result of oral exposure. CAG based its conclusions (63) on the facts that oncogenic changes were reported in several different mouse strains and that tumors with lung metastases had been reported by Thorpe and Walker (58).

Another bioassay study on the oncogenic effects of lindane has been performed by the National Cancer Institute (NCI), as part of its Bionetics-II program for the evaluation of compounds suspected of carcinogenic activity. A rat study was commenced on September 7, 1971; animals were sacrificed after October 9, 1973. A mouse study was commenced on January 4, 1972; animals were sacrificed after September 25, 1973. NCI has not issued a final report with respect to these studies. However, preliminary data was submitted to EPA concerning these studies bearing the notation "Incomplete-not verified." This preliminary data reflects, among other things, pathological diagnoses of tissue sections taken from the animals in the studies and some statistical analyses of the results. Because of the existence of completed studies which provided an sufficient basis for presuming against the registrations of lindane products on the basis of oncogenic effect, the preliminary results of the NCI study were not submitted for formal comment by either CED or CAG, and are not a basis for issuance of a rebuttable presumption against registration in this instance. However, EPA is interested in receiving comments from registrants or other interested persons concerning the significance which should be accorded to the preliminary data which have been received with respect to this NCI study. For this reason, the preliminary data are attached (115).

(a) Studies in Which Dietary Gamma-BHC Produced Oncogenic Changes in Rodents

All laboratory studies in which observed oncogenic changes took place used mice as the test animals. Goto et al. (60) fed 5-week-old male mice (strain ICR-JCL) 300 or 600 ppm gamma-BHC for 26 weeks. Liver tumors were observed in 50% of 10 animals ingesting 600 ppm gamma-BHC. Histologically, the nodules were classified as benign hepatomas. Although the investigators found no metastasis to lymph nodes or other internal organs, there was no indication that the lungs had been serially sectioned, the most reliable method of detecting metastases. Another change associated with gamma-BHC feeding was a two-fold increase in the ratio of liver weight to body weight. Also, five treated animals (25%) died early in the study. There was no microscopic or macroscopic indication of tumor development and no increase in the liver-to-body weight ratio for the animals ingesting 300 ppm gamma-BHC.

Hanada et al. (64) treated 6-week-old male and female mice (strain dd) with 100, 300, or 600 ppm gamma-BHC for 32 weeks; the animals were then maintained on a basal diet for 6 weeks and sacrificed 38 weeks after feeding started. Tumors were found in 4 of 7 females and in 3 of 4

males ingesting 600 ppm gamma-BHC for a combined rate of 64% (7 of 11). None of the 29 control animals, the 18 animals ingesting 100 ppm, nor the 16 animals ingesting 300 ppm gamma-BHC bore tumors. Doses of 300 ppm gamma-BHC produced atypical proliferation of liver cells.

Thorpe and Walker (58) fed four-week-old male and female mice (strain CFI) 400 ppm gamma-BHC for 52 to 110 weeks. They reported a statistically significant increase in the incidence of hepatic tumors as well as metastases to the lung in the gamma-BHC-fed animals relative to the controls: 96% of the males had tumors including 11% metastases, and 95% of the females had hepatic tumors with no metastases. Hepatic tumors were found in 24% of the control animals, but no metastases were observed in this group.1/ Other observations included toxic effects leading to death during the first three months of lindane-feeding for approximately 15% of the animals. Further, for the entire 110-week experimental period, there was a 90% total fatality record for gamma-BHC-fed animals as compared to 68% for the control group.

(b) Studies Reporting No Observed Oncogenic Effects

(i) Mouse Studies

Nagasaki et al. (61) fed 20 male mice (strain dd) 100, 250, or 500 ppm gamma-BHC for 24 weeks, and Ito et al. (66) fed male mice (strain dd) 100, 250, or 500 ppm gamma-BHC for 24 weeks. None of the control or gamma-BHC-fed animals developed tumors in either of these studies.

Herbst et al. (59) fed NMRI mice 12.5, 25, or 50 ppm gamma-BHC for 80 weeks. The authors reported benign hepatomas in 5 of 195 control animals and in 4 of 292 lindane-fed animals. Gamma-BHC feeding alone or in combination with polychlorinated biphenyls (PCBs) had no effect in male mice ingesting these compounds for 24 weeks.

1/ In this study primary tumors were found at extrahepatic sites, primary lung and lymphatic tissue, in 82% of the control animals. A compilation and analysis of CFI mouse tumor data by Sher (65) from several different studies showed that this strain has a high spontaneous tumor rate at extrahepatic sites. The Sher compilation also showed that in four different studies approximately 75% of the spontaneously forming tumors were found in tissues other than liver and that spontaneously forming liver tumors were found in approximately 25% of the animals. The Thorpe and Walker data are consistent with these data showing that the CFI strain has a spontaneous tumor rate at extrahepatic sites approximately three times greater than the rate in liver tissue.

(ii) Rat Studies

Several studies reported that lindane-feeding did not cause oncogenic changes. In a lifetime exposure study Fitzhugh et al. (67) fed Wistar rats 5 to 1,600 ppm lindane for approximately two years. At doses of 5 to 800 ppm, no macroscopic or microscopic changes were reported in the tissues examined; the organs of some experimental animals were not examined microscopically. At 800 to 1,600 ppm toxic effects reduced the lifespan of some animals and led to two-fold increases in liver weight and "slight" or "moderate" liver damage such as enlarged liver cells, fatty degeneration, and necrosis in the survivors. In another lifetime study, rats ingesting 25, 50, or 100 ppm gamma-BHC showed no significant increase in tumor incidence relative to the controls (68).

Ito et al. (69) fed male Wistar rats 500 ppm gamma-BHC for 24 or 48 weeks. Liver cell hypertrophy was observed after 48 weeks, but no tumors were found in the BHC-fed animals. Ortega et al. (70) fed Sherman rats 50 or 100 ppm lindane for 40 weeks. Liver cell hypertrophy was reported for some animals, but no tumors were found.

(2) Reproductive and Fetotoxic Effects in Mammalian Species[1/]

40 CFR 162.11(a)(3)(ii)(B) provides that "a rebuttable presumption shall arise if a pesticide's ingredient . . . (p)roduces any other chronic or delayed toxic effect in test animals at any dosage up to a level, as determined by the Administrator, which is substantially higher than that to which humans can reasonably be anticipated to be exposed, taking into account ample margins of safety." This section reflects concern that chronic exposure to chemicals may result in injury to the reproductive system and/or the fetus and provides that a rebuttable presumption shall arise if chronic chemical exposure in test animals produces such results.

1/ Chronic reproductive effects in avian species are discussed in Section III.D.(2).

Several studies, detailed below, report that exposure to lindane prior to or during mammalian gestation produced embryotoxic or fetotoxic effects in test animals. These effects included reductions in the size of offspring, delayed and retarded sexual maturation, and increased frequencies of stillbirths among the offspring of lindane-exposed dams. In these studies some effects were observed at most dosage levels tested, but the lowest dose at which these effects may be observed is not known; nor is it known whether the levels which produced fetotoxic effects in these studies are substantially higher than those "to which humans can reasonably be anticipated to be exposed." In the absence of an established level at which there was no demonstrated effect and with a subsequent lack of basis for choice of an "ample margin of safety," it may be presumed that current exposure is sufficient to produce reproductive and fetotoxic effects in humans. Accordingly, the Working Group recommends that a rebuttable presumption be initiated pursuant to Section 162.11(a)(3)(ii)(B).

(a) Growth, Maturation, and Reproductive Capacity in Rats

Naishtein and Leibovich (71) described delayed initiation of the first estrus in pubescent rats and longer interestrous periods in the offspring of female rats (mongrel) which had been fed 0.5 mg/kg lindane for four months prior to mating and pregnancy. Lindane-fed animals averaged 4.07 cycles per month as compared to 6.14 cycles in control animals ($p<0.05$); test animals also averaged a 4.8 day diestrus as compared to 1.9 days for the control animals ($p<0.05$). These observations indicated that the offspring of lindane-fed females have fewer estrous cycles during their lifetimes and suggested that the reproductive capacity of the new generation will be reduced accordingly. Treatment with a mixture of lindane (0.02 mg/kg) and DDT (0.05 mg/kg) and with DDT alone (0.02 mg/kg) produced similar results, but treatment with low doses (0.05 mg/kg) of lindane alone had no statistically significant effect. The authors stated that the pesticide concentrations used in these experiments were similar to those occurring in water, food, and soil.

In addition, this report included a graph which showed that at the age of one month the offspring of lindane-fed mothers weighed 25% less than the offspring of control animals. This suggests that maternal exposure to lindane retards growth of fetal and/or newborn rats. The authors also stated that exposure to lindane increased the number of stillbirths and reduced viability of the surviving offspring. The report did not include the numerical data which formed the basis for these conclusions.1/

Petrescu et al. (73) examined the effects of lindane on the reproductive capacity of four successive generations of rats; 327 rats in the P, F1, F2, and F3 generations were studied. The investigators reported that 5, 10, or 15 mg/kg lindane in the diet lengthened the average duration of pregnancy from 21 to 22 days in the control animals to 21 to 24 days in the lindane-fed animals and that in the 15 mg/kg group there was a decreased fertility index (the number of births relative to the number of animals in the parental population) from 100 births per control parental population to 60 births per parental population in the group ingesting lindane. The report also described dose-dependent delayed opening of the vagina and delayed initiation of the first estrus in the offspring of lindane-fed mothers, as well as longer cycles in the F2 and F3 generations. These indications of retarded sexual maturation and depressed sexual function suggest that exposure to lindane during pregnancy reduces the reproductive capacity of lindane-treated parents and represses sexual maturation in subsequent generations.

1/ Dr. K. Dianne Courtney, an EPA scientist has evaluated this study. Dr. Courtney reported that the study indicated that the increased mean duration of the estrous cycle was primarily due to increased intervals between cycles. She noted it was difficult to determine from the numbers presented whether or not the incidence of stillbirths had increased.

Dr. Courtney also observed that because no standard deviations were presented and data was not seperated by sex it is difficult to judge whether the growth rate of neonates was reduced in the high dosage group (72).

The study also reported a progressive increase in the proportion of stillbirths with each successive generation. In the F1 generation there was 1 stillbirth per 104 births in animals ingesting 5, 10, or 15 mg/kg lindane and no stillbirths per 50 births in the control animals. In the F2 generation there were 25 stillbirths per 64 births in the lindane-fed groups, and 1 stillbirth per 45 births in the control animals. In the F3 generation there were 3 stillbirths per 6 births among the survivors in the lindane-fed groups, and no stillbirths per 56 births in the controls. In addition, spastic paraplegia was observed in 17 of 119 F1 and 7 of 52 F2 animals but not in the parental groups (14 controls, 34 experimentals) nor in the F2 and F3 control groups (32 and 28 animals, respectively). These data indicated that exposure of rats to lindane during pregnancy increased the incidence of abnormal and stillborn offspring[1/].

(b) Reproductive Capacity, Teratogenesis, and Stillbirths in Dogs

Earl et al. (74) reported that dietary lindane administered during pregnancy had no significant adverse fetotoxic or teratogenic effects on beagle puppies (Table 1). Pesticide feeding began on day 1 or day 5 of gestation at levels of 7.5 or 15 mg/kg/day. Lindane-feeding had minimal effects on litter size and on the incidence of pregnancy, resorptions, and teratogenesis. However, lindane-feeding did increase the proportion of stillborn animals. The incidence of stillbirths in the control group was 2%; the frequency of stillbirths increased to levels of approximately 18, 23, and 30% in 3 groups of dogs ingesting lindane at either 7.5 or 15 mg/kg/day during pregnancy.

1/ Dr. Courtney reviewed this study also and concluded that the researchers' findings were valid indicators of lindane's adverse effects on normal reproductive functions. She noted, however, that not all details of the experimental design were specified and that this precluded complete analysis of some data. Despite the reporting limitations, Dr. Courtney concurred in the conclusion that lindane significantly affected the duration of pregnancy and decreased the fertility index. Moreover, she stated that there was a progressive increase in the mortality rate in the three generations due to a fetotoxic and/or reproductive effect. Dr. Courtney noted that the observations of paraplegia in the F1 and F2 generations "was probably quite real" (72).

Table 1. EFFECT OF DIETARY LINDANE ON REPRODUCTIVE CAPACITY IN DOGS

Parameter / Protocol	% Pregnant	% Resorption	Average Puppies/ Litter	% Pups with Terata	% Stillborn
Control	87.5	5.1	4.8	1.0	2.0
7.5 mg/kg/day beginning day 1	100.0	0	4.4	0	22.7
7.5 mg/kg/day beginning day 5	85.7	3.3	4.8	1.6	30.5
15 mg/kg/day beginning day 5	84.6	2.9	6.1	0	17.9

Source: Earl et al. (74).

B. Acute Toxicity: Hazards to Wildlife

40 CFR Section 162.11(a)(3)(i)(B) sets forth criteria for which a rebuttable presumption may arise because of the pesticide's acute toxicity to wildlife. As discussed in the preamble to 40 CFR Part 162 (40 FR 28262), pesticides which meet or exceed the acute toxicity criteria of Section 162.11(a)(3)(i)(B) must be closely scrutinized to determine if the hazard presented by the pesticide's acute toxicity necessitates restrictions on use, or denial or cancellation of the registrations.

(1) Aquatic Species

Section 162.11(a)(3)(i)(B)(3) specifies that a rebuttable presumption shall arise against a pesticide use for direct application to water if such use when applied to a 6-inch layer of water would result in concentrations more than 1/2 the acute LC_{50} for aquatic organisms likely to be exposed. Data indicate that certain pesticide products[1/] containing lindane labeled for use against mosquito larvae meet or exceed the acute toxicity criteria for representative fish and crustaceans.

1/ At least two currently registered products have label directions for use in aquatic environments against mosquito larvae (75). Registrants for these two products have requested deletion of this use from their labels. Given the number of lindane registrations, there is always the possibility of Agency computer or record keeping errors. This requires the initiation of a rebuttable presumption on this effect so that all registered lindane product labels with direct water-use may be acted upon. Formerly, lindane was also registered for rice seed treatment in aquatic environments.

To determine whether lindane-use in estuarine/marine environments meets rebuttable presumption criteria, CED utilized the indicated LC_{50} values for the following representative estuarine/marine species:1/

species	lindane 96-hour LC_{50} values
Pink shrimp Penaeus duorarum	0.17ppb2/
Grass shrimp Palaemonetes pugio	4.44ppb
Mysid shrimp Mysidopsis bahia	6.28ppb
Sheepshead minnows Cyprinodon variegatus	103.9ppb
Pinfish Lagodon rhomboides	30.6ppb

Calculations based on these values (76) indicate that any application of lindane to estuarine/marine waters greater than 0.000116 lb/acre would be expected to exceed 1/2 the 96-hour LC_{50} in a 6-inch layer of water for pink shrimp, the species with the lowest LC_{50} among representative species.

1/ Test results from Schimmel et al. (76).

2/ The LC_{50} is here expressed as the concentration of toxicant in the environment measured in parts per billion (ppb).

To determine whether lindane-use in fresh water environments meets rebuttable presumption criteria, CED utilized the indicated LC_{50} values for the following representative fresh water species:1/

species	lindane 96-hour LC_{50} values
Channel catfish Ictalurus punctatus	44ppb
Black bullhead Ictalurus melas	64ppb
Goldfish Carassius auratus	131ppb
Fathead minnow Pimephales promelas	87ppb
Carp Cyprinus carpio	90ppb
Redear sunfish Lepomis microlophus	83ppb
Bluegill Lepomis macrochirus	68ppb
Largemouth bass Micropterus salmoides	32ppb
Rainbow trout Salmo gairdneri	27ppb
Brown trout Salmo trutta	2ppb
Coho salmon Oncorhynchus kisutch	41ppb
Yellow perch Perca flavescens	68ppb

1/ LC_{50} in parts per billion; test results from Macek and McAllister (76).

Calculations based on these values (76) indicate that any application of lindane to fresh water greater than 0.00273 lb/acre would be expected to exceed 1/2 the 96-hour LC_{50} in a 6-inch layer of water for brown trout, the species with the lowest LC_{50} among representative species.

The foregoing data and calculations establish that the recommended applications for lindane products registered for aquatic use exceed the acute toxicity criteria of Section 162.11(a)(1)(B) for representative fresh and salt water species. Accordingly, a rebuttable presumption is declared against the registration of lindane products labeled for this or any other direct application to water which exceeds the 0.00273 lb/acre rate.

While there appear to be no other lindane products with registered aquatic uses, other registered non-aquatic uses may result in lindane-contamination of aquatic environments: for example, drift from uses such as aerial application to control mosquitoes, runoff into bodies of water, or application to farm animals which subsequently wade into a body of water. Further, although the Agency is not aware of any recent major fish kills attributable to direct lindane use, there are PERS reports[1/] alleging fish kills resulting from uses of lindane other than direct application to water. PERS reports include lindane-associated fish kills caused by runoff from a mushroom house, overtreated cattle wading into a pond, and an unspecified aerial application (77). In addition, a 1976 report to EPA's Office of Water Planning and Standards noted a kill of 230 trout after sheep treated with a mixture of lindane and toxaphene waded into a creek (78). Fish kills reported to the Agency often do not specify the pesticide or even the type of chemical responsible. These data, therefore, probably underestimate the actual effects of lindane use.

1/ The agency maintains a Pesticide Episode Reports System (PERS) which collects reports of pesticide exposure affecting humans, domestic animals, livestock, and wildlife.

Holden (79) reported that fish mortalities due to accidental or careless discharge of sheep dipping fluid into streams occurred every year in Scotland. High residues of both dieldrin and lindane were found in 26 brown trout killed in this manner. It should be noted that lindane's water solubility and volatility result in a relatively rapid disappearance of most of the lindane applied to water.

Other water contamination problems may be associated with the use of lindane for animal treatment. For example, land-disposal of sheep dips containing persistant pesticides including lindane rendered the waters of Chew Valley Lake in England temporarily unpotable (80). An investigation of pesticide use on nearby farms and analyses of mud samples implicated the infiltration of unused sheep dip spilled on the ground into an underground storage system as the cause of death or prevention of reproduction of crustaceans which had previously controlled algae.

(2) Avian species

As noted previously in section I.A.(2)(d) and III.D.(1), residues of lindane have been found in certain birds in this country. The use of lindane on crops and seeds prompted the Criteria and Evaluation Division to comment upon the potential acute risk to birds. CED concluded that bird LC_{50} values are generally well in excess of expected feed residues of lindane for crops (81).

III. OTHER RELEVANT ADVERSE EFFECTS

This section addresses certain criteria for determination of unreasonable adverse effects which lindane may produce, but for which insufficient evidence exists to initiate a rebuttable presumption.

A. Mutagenic Effects

Section 162.11(a)(ii)(A) provides that a rebuttable presumption shall arise if a pesticide's ingredients(s), metabolite(s), or degradation product(s) induce mutagenic effects, as determined by multi-test evidence. Several investigations of lindane's mutagenic capacity appear in the scientific literature. Tests for point mutations performed in microbial systems and with Drosophila melanogaster are negative, indicating that lindane does not cause point mutations. In several of the customary animal and plant test systems for chromosomal aberrations, lindane acts as a mitotic inhibitor and has been shown to produce changes in ploidy. However, mitotic inhibitors are not usually classified as mutagens, and the evidence is not sufficient to classify lindane as a chromosonal mutagen (82). Thus existing data do not establish that lindane is a mutagen, and there is no rebuttable presumption on this ground.

B. Hemotoxic Effects in Humans

40 CFR 162.11(a)(6) provides that the Administrator may decide to cancel a pesticide or to hold a hearing if the pesticide poses a substantial question of safety to humans or the environment "based on toxicological data, epidemiological studies, use history, accident data, monitoring data, or such other evidence as is available." Accordingly, data on lindane's use and accident history which suggest that lindane may produce hemotoxic effects in humans will be included in the notice of rebuttable presumption against registration but not used as a basis for the rebuttable presumption.

Several reports in the medical literature indicate that lindane may be a primary or contributing factor in the development of several human blood dyscrasias, particularly aplastic anemia and possibly leukemia. These reports, summarized below, are based upon medical case histories in which human exposure to lindane, both from normal use and from accidental overexposure, appeared linked to subsequent development of bone marrow and blood disorders. Although the number of cases is relatively small and the incidence of disease appears to depend more on individual susceptibility than on exposure per se, the Working Group believes that the evidence is sufficient to warrant Agency consideration of lindane's possible hemotoxic effects. Moreover, these reports of lindane-associated hemotoxic effects in humans are consistent with medical reports indicating that other chlorinated hydrocarbon pesticides such as DDT and chlordane may be hemotoxic in humans, inducing bone marrow and blood disorders (83), (99), (100).

For these reasons, the Working Group recommends that the Agency solicit comments on the available evidence and request submission of any additional cases or relevant information. In view of the infrequent but nonetheless persistent reports of lindane-associated hemotoxicity in only a small portion of persons who have been regularly exposed to lindane, the Working Group also recommends that the Agency particularly solicit comment on the questions of individual sensitivity to lindane and the epidemiology of lindane-associated hemotoxic effects. The Working Group is not aware of definitive animal studies in which lindane-related hemotoxic effects have been observed, and the medical literature indicates that there are no reliable animal tests for confirming or denying the reports of hemotoxic effects in humans. We therefore recommend that the Agency also solicit information on animal test systems in which lindane-related hemotoxicity has been or could be assayed.

(1) Blood Dyscrasias Associated with Exposure to Lindane Only

(a) Aplastic Anemia and Hypoplastic Bone Marrow

West (83) summarized the medical case histories of five California residents who developed aplastic anemia following exposure to Lindane. In each case the patient was exposed to lindane that was used for pest control purposes and became ill for nine days to a year. Two of the patients were exposed through lindane home vaporizers,[1/] two were exposed to lindane which had been sprayed in their homes, and the fifth patient was accidentally engulfed in a cloud of lindane being sprayed in a relative's yard. A diagnosis of aplastic anemia was made in each case, and aplastic anemia or hypoplastic bone marrow was listed as a cause of death in four of the five cases.

Vodopick (84) described aplastic anemia in a two-year-old child who was exposed to lindane during a three-month period in which a preparation containing lindane was used to treat the family dog for mange. The patient had no known exposure to any other known hemotoxic agent. When the mange treatment was discontinued following determination of the lindane source, the child recovered. Woodliff et al. (85) described a similar case in Australia. A woman who had washed her dog each week for two years in a 2% lindane solution was diagnosed as having bone marrow hypoplasia, "probably consequent upon exposure to lindane." She died three months later.

1/ As observed in Section II, several "one-shot" lindane vaporizers are still being produced and sold.

PERS Report 71-173 described a case in which a 79-year-old woman developed aplastic anemia after she "made an error" while using a spray containing lindane against a hornets' nest in her home and sprayed herself in the eye. She first sought medical treatment five days later. Two months after the spraying incident her condition was diagnosed as pancytopenia with severe anemia and severe thrombocytopenia. She died three months after exposure. The immediate cause of death was a cerebro-vascular accident with thrombocytopenia and toxic aplastic bone marrow listed as secondary factors. The medical reports described hemotoxic effects only and did not indicate any damage to the eye or skin (86).

Samuels and Milby (87) studied the effects of lindane exposure on 79 California residents who had been regularly exposed to lindane in their homes or businesses, and a companion study (112) compared a small sample (40 persons) which had been occupationally exposed to lindane with a sample which had not. The first study reported lindane-associated changes in five blood parameters (lindane content, blood creatine level, reticulocyte count, white blood cell count, and polymorphonuclear leukocyte count), but there was no evidence of pancytopenia with reticulopenia, a key indicator of hypoplastic or aplastic anemia. Specifically, none of the changes exceeded the normal range, and there was no illness attributable to hematological disorder. These investigators did note, however, that some observations were sufficiently "bizarre" to require a conclusion that the hematopoietic system was not "entirely normal" in a few subjects.

(b) Other Blood Dyscrasias

Medical reports have linked lindane to other blood dyscrasias in persons who have had no known exposure to any other known hemotoxic agent. In the report described above, West (83) listed the case of a child exposed to a lindane home vaporizer for over a year. After an initial "tentative diagnosis of atypical leukemia" her condition was later described as a "serious blood dyscrasia." She recovered after the vaporizer was removed. Also, as reported above, Samuels and Milby noted unusual and unclassifiable hematologic findings in a few of the subjects in their study. 1/

1/ In a study of lindane's possible fetotoxic effects, Petrescu et al. (73) reported that dietary lindane (5, 10, or 15 mg/kg) did not affect the blood or bone marrow in experimental rats.

(2) Cases Involving Exposure to Lindane in Combination With Other Chemicals

(a) Aplastic Anemia and Hypoplastic Bone Marrow

There are some reports of aplastic anemia attributed to exposure to lindane and/or another possible hemotoxic agent. Albaharay et al. (88) described the case of a sanitation department employee who developed "panmyelopthisis"[1/] 9 days after exposure to DDT and lindane. Similarly, a teenage boy developed a fatal case of aplastic anemia after being exposed to lindane and DDT for two months while working on a California farm (89). The clinical diagnosis was, in part, "aplastic anemia due to insecticides." In discussing this case at a Barnes Hospital Clinical Pathological Conference, Dr. Shank stated his belief, based upon his review of th medical literature and case reports, that lindane rather than DDT was more probably the responsible hemotoxic agent (89).

PERS Report 71-183 (90) described a case of fatal aplast anemia in an Oregon farmer who was exposed to lindane and toxaphene via the inhalation and dermal routes while spraying cattle in April 1969. He was treated for respiratory symptoms for nearly a year following the onset of illness. In September 1970 his condition was diagnosed as aplastic anemia secondary to lindane and toxaphene exposure. The autopsy report identified the cause of death as (1) acquired aplastic anemia due to lindane and toxaphene exposure and (2) acute myelomonocy leukemia secondary to condition (1).

(b) Other Blood Dyscrasias

The medical literature includes reports of other bone marrow and blood disorders following simultaneous exposure to lindane and another hemotoxic agent. Jedlicka et al. (91) described two 20-year-old cousins who lived and worked together and who, after simultaneous exposure to lindane and DDT, both developed paramyeloblastic leukemia. The authors concluded that exposure to lindane caused the

1/ Dorland's Medical Dictionary describes this condition as "general aplasia of the bone marrow."

leukemia in these cases. Hoshizaki et al. (92) also reported a case of leukemia in a sanitation department employee who was regularly exposed to DDT and lindane.[1/]

(3) Epidemiological Considerations

The importance of the foregoing observations of lindane-associated hemotoxicity is somewhat limited by the relatively small number of cases. This prevents evaluation of these reports in accordance with customary statistical and epidemiological criteria and thus precludes determination of whether there is or is not a cause and effect relation between lindane exposure and blood dyscrasias. A second factor preventing definitive studies is the lack of a suitable animal model for experimentation .

After reviewing several of the reports cited above, Dr. Jack Griffith of EPA wrote that "none support the contention that exposure to....lindane results in human blood dyscrasias." He qualified this conclusion by stressing that the data base was inadequate and that the methodology for making these determinations is limited (97).[2/]

The medical case histories summarized here and elsewhere do not satisfy epidemiologic criteria for establishing a cause and effect relationship between lindane and blood dyscrasia. Reports describing simultaneous exposure of several people to lindane followed by the development of clinical symptoms in only one of the persons so exposed suggest that adverse reaction to lindane is highly individualized. For example, in the report of the child who developed aplastic anemia after the use of a lindane product to control the family dog's mange, neither the child's 9-year-old brother nor his father exhibited symptoms even though they too were exposed to the treatment mixture (84). In West's first case, three family members were exposed to the pesticide in their home, but only one person developed aplastic anemia. Further, the child in West's third case was exposed while playing in a neighboring child's home, but there is no indication that this child, who presumably was exposed to a

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1/ Other similar cases in which lindane may be a factor are not included here because the published reports refer only to "benzene hexachloride" (BHC) and do not specify whether the term refers to lindane, the gamma isomer of BHC, or to technical grade BHC which is a mixture of BHC isomers. See, for examples, Gewin (93) and Danapoulous (94).

2/ See also Zavon (95), who contests reports of lindane's hemotoxicity and Hans (96), who disputed Dr. Zavon's evaluation.

greater extent than her visitor, developed any symptoms. In another case diagnosed as "atypical leukemia" other members of the family did present "abnormal" blood counts and "mild anemia" (83).

Occupational exposure to lindane has been linked to bone marrow dyscrasias in people who worked with lindane shortly before developing symptoms (88), (89), (91), (92), (98), (113). However, Samuels and Milby (87) in a systematic investigation of 79 persons exposed regularly to lindane did not uncover any significant hematological disorders. These investigators did note, however, that if lindane-associated hematological disturbance is dependent on individual characteristics such as rare sensitivity or genetic predisposition, their study would not have detected this effect because of the small sample population. Other physicians and scientists have also commented that lindane's adverse effects may depend on individual sensitivity.

C. Acute Hazards to Humans and Domestic Animals

Section 162.11(a)(3)(i)(A) provides that a rebuttable presumption shall arise if the pesticide as formulated has an acute dermal LD_{50} of 40 mg/kg or less, if the pesticide has an acute dermal LD_{50} of 6 g/kg or less as diluted for use in the form of a mist or spray, or if the pesticide has an inhalation LC_{50} of 0.04 mg/liter or less as formulated. The Working Group is currently reviewing acute dermal and inhalation data for the 641 lindane products either federally registered or for which federal registration has been sought. Data gaps exist. A number of these products contain other pesticides as active ingredients in addition to lindane. The hazard posed by products with several active ingredients may differ markedly from products labeled for the same use which contain only lindane as an active ingredient. The Working Group recommends that each registrant be directed to certify to the Agency the registrant's determination as to whether or not the formulation as well as each dilution registered for use meet or exceed the acute toxicity criteria above. The certification must specify the acute LD_{50} or LC_{50} of the formulation and the calculations or data relied upon in making that determination. In addition, the RPAR notice should solicit relevant data on these effects from all sources. Should any of the above criteria be exceeded by a lindane product, the rebuttable presumption should be extended to include issuance on the basis of acute dermal and/or inhalation effects of any product exceeding these criteria.

As observed previously the Agency maintains a Pesticide Episode Reports System (PERS) which collects and tabulates reports of pesticide exposure involving humans and domestic animals.

A review of PERS data for all episodes reported between 1966 and June 15, 1976, which implicated products containing lindane has disclosed 84 incidents involving humans and 15 incidents involving domestic animals. "Incidents" include all association with a given pesticide and do not always imply ingestion.

Seventy-seven of 84 human incidents were reported to have occurred in the home. Of the 84 human episodes, 49 reports listed lindane alone and 35 listed lindane in combination with another active ingredient. The majority of the lindane-only cases involved children, and in twenty-four of these cases the child ingested the pesticide. Exposure to lindane led to clinical symptoms in half of the lindane-only reports; hospitalization followed by death occurred in five of the reported episodes. Many reported ingestions of lindane by children were of lindane pellets for use in the now cancelled continuous vaporizers.

In contrast to lindane alone, the majority of the incidents resulting from exposure to lindane in combination with another pesticide involved adults. Twenty-one of these incidents occurred in the home. Clinical symptoms were listed for less than half of these cases, and two cases resulted in death.

Fifteen livestock or domestic pet incidents were reported. In nine of these cases lindane alone was was implicated; lindane was present in combination with another active ingredient in the remaining six cases (77). The PERS data does not, however, necessarily include all incidents which have occurred during the given time span.

D. Population Reductions in Nontarget Organisms

Section 162.11(3)(ii)(C) provides that a rebuttable presumption shall arise if a pesticide's ingredient(s), metabolite(s), or degradation product(s) can reasonably be anticipated to result in significant local, regional, or national population reductions in nontarget organisms, or fatalities to members of endangered species. This provision reflects concern that pesticide contaminants in air, water, soil, and food supplies may adversely affect the reproductive efficiency of natural populations. Under this section, the Agency may consider a pesticide's potential for accumulation

in the environment, and its capacity for producing chronic effects which can reasonably be anticipated to lead to population reductions. We recommend that the Agency not presume against lindane on this basis at this time, but seek in the Notice of Rebuttable Presumption information which will permit complete assessment of lindane's potential for producing population reductions, particularly among avian wildlife.

This rebuttable presumption criterion is based on scientific studies which suggest that another organochlorine pesticide, DDT, adversely affected natural avian populations through the action of its metabolite, DDE, on avian eggs. In one study, Ratcliffe (101) reported that a decrease in eggshell thickness in natural raptor populations in Britain "coincided closely" with the post-World War II introduction of DDT into general usage. Risebrough and Anderson (102) established that feeding 40 ppm DDE to experimental mallard populations reduced eggshell thickness by 17%, and Longcore and Samson (103) reported that 10 ppm DDE in the feed of black ducks led to a 22% reduction in eggshell thickness at the equator.1/

(1) Lindane Residues in Birds

Residue studies have indicated that lindane is present in avian species exposed to lindane in natural and experimental settings (see Section I.A.(2)(d)) and is present in poultry for human consumption (see Section I.A.(2)(e)). This demonstrates that lindane can and does accumulate in avian tissues and eggs, thereby presenting the potential for causing population reductions in avian wildlife.

We recommend that the Agency solicit additional information on lindane's possible long-term chronic effects on avian wildlife based on several separate studies which report that lindane residues are present in tissues and eggs of wild birds, indicating that such populations may be exposed to and may accumulate lindane and that exposure to lindane may increase embryonic mortality in birds. These observations suggest that pesticide uses which may significantly contribute to lindane residues in avian eggs may increase embryonic mortality, an effect which would ultimately lead to population reductions.

1/ Other studies suggest that the mechanism involves pesticide interference with hormonal regulation of calcium metabolism and consequent abnormal mobilization of calcium for eggshell formation (104), (105).

(2) Effect on Reproductive Capacity

Sauter and Steele (106) assayed lindane's effects on the reproductive capacity of White Leghorn chickens (Table 2). Following an initial 10-week pre-experimental observation period, hens were fed diets containing 0.1, 1.0, or 10.0 ppm lindane for 10 weeks. Lindane-feeding had no measurable effect on egg fertility. At each treatment level, however, lindane-feeding reduced hatchability and reproductive efficiency, which was defined as the ratio of the number of chicks hatched per hen, with controls set at 100. Further, hens ingesting 1.0 and 10.0 ppm lindane produced eggs which had an early mortality rate (embryonic death between days 1 and 7 of incubation) significantly greater than the controls ($p<0.05$). In addition, the data suggest that lindane-feeding also increased the incidence of embryonic mortality late in incubation (after day 7), but since the control data for the different treatment groups varied, this reported increase was not conclusive.

TABLE 2. EFFECT OF LINDANE-FEEDING ON CHICKEN EGGS AND EMBRYOS

		Control	0.1 ppm	1.0 ppm	10.0 ppm
% Fert.		97.8	97.9	97.9	97.1
% Hatch.		94.4	83.5	83.4	81.9
Reprod. Effic.		100.0	73.9	73.1	66.1
Early Mortality (0-7 days of incubation)	A	2.1	1.1	1.0	1.0
	B		4.9	8.3	10.9
Late Morality (8-21 days of incubation)	A	6.4	9.6	2.1	11.9
	B		11.6	8.3	7.2
Eggshell Thickness (mm)	A	0.37	0.37	0.38	0.36
	B		0.31	0.31	0.33

A. 10-week pre-experimental observation period.
B. 10-week experimental period.
Source: Sauter and Steele (106).

Lutz-Ostertag (107) observed similar lindane-related effects in four successive generations of the Japanese quail. In this study eggs were sprayed with 1.5, 3.0, and 6.0% lindane. The embryonic mortality rate in untreated eggs was 6.06%. After lindane treatment for 14 days, the mortality rates were 16.8% for 1.5% lindane and 20.8% for 3.0% lindane. Further, lindane treatment delayed egg production in the offspring of birds from treated eggs by 8 to 15 days relative to untreated groups. Lindane treatment also reduced maximum egg weights from 15.6g for controls to 14 to 11g in eggs of offspring of lindane-treated birds.

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